IN THE SPECIFICATION

Amend the specification as follows.

Page 1, after the title insert the following new paragraph:

"The contents of the attached CD-R compact discs are incorporated herein by reference in their entirety. The attached discs contain identical copies of a file "620-262.TXT" which were created on the discs on May 24, 2004, and are each 615,372 KB."

AMENDMENTS TO THE SPECIFICATION:

Please amend the paragraph beginning at page 6, line 26, as follows:

In one preferred form the method relates to the EHV-1 ORF30-m1 region marker at amino acid position 752 (based on the V592 numbering - see SEQ. ANNEX 1 (SEQ ID NOs:1-104, consecutively) and SEQ. ANNEX 3b (SEQ ID NO:156)) or one which corresponds to this when sequences are aligned as shown herein (see Table 4).

Please amend the paragraph beginning at page 7, line 30, as follows:

The invention thus employs the identity of a codon at nucleotide positions 2254-2256 or 2278-2280 (based on the EHV-1 V592 numbering - see SEQ. ANNEX 1 (SEQ ID NOs:1-104, consecutively) and SEQ. ANNEX 3a (SEQ ID NO:155)) or one which corresponds to this when sequences are aligned.

Please amend the paragraph beginning at page 16, line 34, as follows:

The invention also provides materials which may be used in the methods disclosed herein. These include isolated nucleic acid molecules consisting of the DNA sequence of EHV-1 (strain V592) ORF30 shown in SEQ. ANNEX 3 (SEQ ID NO:155 and SEQ ID NO:156), which sequence comprises a mutation which reduces the virulence of the gene product.

Please amend the paragraph beginning at page 17, line 1, as follows:

Also provided are isolated peptides comprising, or consisting of, or consisting essentially of, a contiguous portion of at least 10, 15, 20, 30, 40, or 50 amino acids of the amino acid sequence of an EHV-1 strain (preferably strain V592) ORF30 shown in SEQ. ANNEX 3 (SEQ ID NO:155 and SEQ ID NO:156), wherein the portion includes position 752 or 760 of SEQ. ANNEX 3 (SEQ ID NO:155 and SEQ ID NO:156).

Please amend the paragraph beginning at page 17, line 30, as follows:

Preferred primers for the amplification of regions of variable sequence for several ORFs are shown in SEQ. ANNEX 2.(SEQ ID NOs:105-154, consecutively) Of these, the primers for amplification of the ORF30-m1 marker region (ORF30f, ORF30r) and of the ORF68 marker region (ORF68f, ORF68r) are particularly preferred.

Please amend the paragraph beginning at page 23, line 31, as follows:

Where the method involves PCR, or other amplification procedure, any suitable PCR primers may be used. Example primers are described herein. For example primers are shown in SEQ. ANNEX 2 (SEQ ID NOs:105-154, consecutively) Preferred primers are any of those listed as ORF30f, , ORF30r,, ORF68f and ORF68r.

Please amend the paragraph beginning at page 24, line 37, as follows:

Preferred sequencing primers include any of those shown in SEQ. ANNEX 2 (SEQ ID NOs:105-154, consecutively), particularly ORF30s, ORF68s1, ORF68s2 and ORF68s3.

Please amend the paragraph beginning at page 27, line 35, as follows:

During analysis of the V592 sequence data a number of positions were noted where there were differences between the sequences determined from individual sequence templates, indicating that the V592 virion DNA population was heterogeneous at these positions. Each of the regions is listed (numbered according to the V592 genomic sequence, SEQ. ANNEX 1a (SEQ ID NO:1)) and details of the variation noted. NA indicates that the position lies outside of a recognised protein coding sequence (open reading frame: ORF).

Please amend the paragraph beginning at page 28, line 7, as follows:

V592 ORFs which have an altered amino acid sequence compared to the corresponding AB4 ORF are listed. The position of each change is numbered according to the V592 ORF amino acid sequences (SEQ. ANNEX 1b (SEQ ID NOs:2-104, consecutively). For each position, the amino acid sequences for AB4 and V592 are shown. * indicates that the corresponding sequence is absent in the

given strain – i.e. the other strain carries additional amino acids, usually due to variation in copy number of a nucleotide repeat element.

Please amend the paragraph beginning at page 28, line 33, as follows:

Various herpesvirus DNA polymerase sequences were aligned using CLUSTALW (using services at ANGIS, Australia) and the alignment surrounding the EHV-1 ORF30-m1 (D/N_{752})position is shown. Gaps are indicated by dashes (-). Viruses have been grouped as alpha-, beta- and gammaherpesviruses, or unclassified. In each case the abbreviated virus name and sequence accession number are shown (apart from EHV-1 strain V592, reported in this study (SEQ. ANNEX 3b (SEQ ID NO:156))). The first position of each sequence is numbered; where the complete DNA polymerase sequence is not available, numbering of the partial sequence is shown in italics. The position of the D residue conserved in the majority of viruses, corresponding to the ORF30-m1 (aa752) marker position, is shaded.

Please amend the paragraph beginning at page 29, line 25, as follows:

SEQ. ANNEX 1. a) Complete genomic sequence of EHV-1 strain V592 (SEQ ID NO:1); b) Feature table (SEQ ID NOs:2-104, consecutively)

Please amend the paragraph beginning at page 30, line 3, as follows:

SEQ. ANNEX 2. PCR amplification and sequencing primers (SEQ ID NOs:105-154, consecutively)

Please amend the paragraph beginning at page 30, line 9, as follows:

SEQ. ANNEX 3. a) DNA sequence of EHV-1 (strain V592) ORF30 (SEQ ID NO:155); b) Amino acid sequence of EHV-1 (strain V592) ORF30 (SEQ ID NO:156)

Please amend the paragraph beginning at page 30, line 20, as follows:

We determined the V592 genomic sequence (149,430 bp) via shotgun cloning and sequencing of viral DNA prepared from purified virions. Virus supernatant was prepared from equine embryonic lung cells infected at low multiplicity (<0.001 pfu/ml), virions purified by sucrose gradient sedimentation and DNA extracted from purified virions essentially as described by Telford et al [19]. Viral DNA was self ligated, sonicated to generate random fragments and, following end repair, cloned into M13mp19. In addition, a panel of 'semi-random' clones was generated by digestion of viral DNA with frequent cutting (blunt ended) restriction enzymes (AluI, PvuII, BalI), followed by cloning into M13mp19. In the final stages of sequencing, specific regions spanning sequence data 'gaps' were amplified by PCR, blunt ended and cloned into M13mp19. Single stranded M13 templates were prepared and sequenced using proprietory sequencing reagents, and samples analysed on either an ABI 377 or ABI 9600 automated sequencer. Sequence reads were

assembled using the Staden sequence analysis programs PREGAP4 and GAP4 [21]. The complete genomic sequence of EHV-1 strain V592 is shown in SEQ. ANNEX 1 (SEQ ID NOs:1-104, consecutively). It should be noted that the attached sequence is the consensus for the majority of sequence reads. The V592 stock used to generate DNA for sequencing has not been plaque purified and consequently contains a mixture of DNA populations at certain sites. Sites showing heterogeneity between individual sequencing templates are shown in Table 1. These sites are all regions of variable repeat length apart from one position of single nucleotide heterogeneity.

Please amend the paragraph beginning at page 32, line 15, as follows:

In order to test the above hypotheses, we assembled DNA samples prepared from a panel of field isolates (from the U.K. and North America) recovered from outbreaks of varying disease severity, collected over the course of 30 years. A subset of the ORFs with observed coding changes were selected for preliminary analysis, namely ORFs 8, 11, 14, 15, 30, 33, 34, 37, 39, 40, 52, 67, 68, 73. For each of these ORFs, PCR primers were designed for amplification of regions of sequence variability and for sequencing, as listed in SEQ. ANNEX 2 (SEQ ID NOs:105-154, consecutively). PCR products were purified and sequenced (ABI 9600) and the results assembled using the DNASTAR software package. For each ORF region analysed, positions of variable sequence were noted as listed in Table 5.

Please amend the paragraph beginning at page 35, line 23, as follows:

Notably, this is not the case for one of the variable sequences within ORF30. The complete nucleotide and amino acid sequence of EHV-1 strain V592 ORF30 is shown in SEQ. ANNEX 3 (SEQ ID NO:155 and SEQ ID NO:156). Three nucleotide changes are present compared with the AB4 ORF30 sequence (accession no. AAB02465), namely C_{924}-T (non-coding change), G_{2254}-A (amino acid change D_{752}-N) and G_{2968}-A (amino acid change E_{990}-K).

Please amend the paragraph beginning at page 39, line 38, as follows:

The PCR mix (50µl) consisted of 0.3µM of each primer (Genset), 0.2mM of each NTP (Applied Biosystems), 3X PCRx Enhancer solution (Invitrogen) and 1.25U/µl AmpliTaq DNA polymerase (Applied Biosystems) in 10 mM Tris-HCL (pH 8.3) solution containing 1.5mM $MgCL_2$ (Applied Biosystems). The PCR reaction was denatured for 4 min at 94°C, then cycled for 32 cycles at 94°C for 30 seconds, 1 min at the annealing temperature of the primers used, and 2 min at 72°C followed by a final step of 10 min at 72°C. After cycling, 10µl of each PCR product was size fractionated on a 0.7% agarose gel containing ethidium bromide. Following product identification, the PCR products were purified using an Amicon Microcon Filter YM100 kit and quantified by size fractionation, on a 2% agarose gel containing ethidium bromide, with DNA Quantification standards (Whatman Bioscience). The purified PCR products were either cloned into M13mp19 (gap filling for

determination of V592 sequence) or directly sequenced using EHV-1 specific sequencing primers (SEQ. ANNEX 2 (SEQ ID NOs:105-154, consecutively)).

Replace the text of pages 45 and 46 in their entirety with the following:

Table 2 - ORF coding changes between V592 and AB4

ORF	Position [1]	AB4 sequence	V592 sequence
2	59	G	D
5	114	G	V
8	114	D	N
11	189	Q	K
13	305	S	L
	460	A	T
14	619-621	*	PSR 9bp duplication resulting in 3 amino acid insertion
15	166	D	N
22	430	S	P
24	2567-2568	(PTLPPAPPLPQSTSKAASGPP (SEQ ID NO:157))$_2$	*
	2586		126bp deletion (2 copies 63bp repeat element) resulting in 42 amino acid deletion
	2829-2836	G	S
		*	AKDQAKDQ (SEQ ID NO:158)
	2904		24bp insertion (2 copies 12bp repeat element) resulting in 8 amino acid insertion
	2913-2927	E	K
		*	PTGAVPENTPLPDDS (SEQ Id NO:159)
	3099		45bp insertion resulting in 15 amino acid insertion
		T	A
29	12	T	K
30	752	D	N
	990	E	K
31	90	N	S
32	42	S	L
33	15	N	H
	976	N	D
34	66	D	G
36	47	S	R
37	265	A	V
39	440	S	L
40	196	R	H

42	1275	K	R
45	427	E	G
46	140	F	S
50	367	P	S
52	386	A	V
57	804	K	R
64	73 648	T T	A S
67	261	S	F
68	210 247	R D	H M – due to single nucleotide (C) deletion resulting in frameshift relative to AB4. All downstream sequence divergent from AB4. Resulting polypeptide 303 amino acids long (cf. 418 for AB4)
71	226-227 231-299	SS *	TA TAATTTAATTSSATTAATTSS(TTTAA)$_9$TTT (SEQ ID NO:160) additional copies 15bp repeat elements and nucleotide substitutions, resulting in 69 amino acid insertion[2].
73	122	A	V
76	128	F	S

1 Numbered according to the V592 amino acid sequence.

2 Variable copy number in V592 – majority sequence shown

Replace the entirety of Table 4 on page 48 with the following new Table 4:

Table 4 - Amino acid sequence alignment for herpesvirus DNA polymerases (SEQ ID NOs:161-197, consecutively)

Virus	Accession		
ALPHA			
EHV-1 V592		738	ALDEVDLAGLQPS-----VNYSTFEVGDQK-LFFVHAHIRESLL
EHV-1 AB4	P28858	738	ALDEVDLAGLQPS-----VDYSTFEVGDQK-LFFVHAHIRESLL
EHV-4	AAC59546	739	ALNEVDLAGLQPC-----VDYSTFEVGDQK-LFFVHAHIRESLL
BHV-1	CAB01595	770	VRREAAPAGLTPG-----ADYATFDVGGRA-LHFVRAHVRESLL
BHV-2	AAD55134	739	ALDAEAVGGLEAG-----RDYMEITVGGDT-VYFVKAHVRESLL
FeHV-1	CAA12264	727	TTERQSLETLRPG-----IDFSEFDVGGHK-LYFVDSHVREEPA
VZV	P09252	702	TLNFETVKRLNP------SDYATFTVGGKR-LFFVRSNVRESLL
SimVZV	AAG27201	688	AFDIESVKHLGS------NDYSVFNVGGQQ-LFFVHAHIRESLL
PRV	AAA74383	593	ALAR--PAGLRE------DEFSAFEVNGER-LYFVHAGVRESLL
HSV-1	P09854	737	SLRADAVAHLEAG-----KDYLEIEVGGRR-LFFVKAHVRESLL
HSV-2	P07918	742	SLRPEAVAHLEAD-----RDYLEIEVGGRR-LFFVKAHVRESLL
MDV-1	AAG14223	718	VHDDTNLSNLRPQ-----DDYLEINVQGKL-LRFVKPHIRESLL
MDV-2	BAA78719	690	INDDRKLADLRPR-----DDYMEIDVQGKS-LHFAKPHIRESLL
HVT	AAG45768	703	LPAGTIINDLRRG-----DDYIEIDVQGSI-LRFVKPHIRESLL
BETA			
HCMV	DJBEC1	737	LVPGGEYPVDP-------ADVYSVTLENGVTHRFVRASVRVSVL
MCMV	AAA45940	644	LVE--GSPEVP------EKDVLRVEIGDQC-HRFVRENVHRSLL
RCMV	Q85428	670	LVD--GSPPVP------DEDVLEVVVGEATRYRFVREHVRRSLL
PorcCMV	AAF80109	587	ILNDEDVTGID------EKDILTVHVNKNTVYRFVRSGVRESML
RhCMV	AAC05256	611	VAPGGESPPE--------SDVLTVELESGLSYRFVKNTVRNSVL
GPCMV	Q69025	666	LPL--GRDDG-----LSDDDVFLLEFDDGTRYGFVREHVRKSIL
ElephHV-1	AAG41999	625	ITDNYVASLR-------EEDITMVTTNTGRVHRFVKPHVRKSIL
HHV-6	NP_049231	592	VLDERQIAGLS------ESDILTVKLGD-ETHRFVKPCIRESVL
HHV-7	AAC40752	592	VVDENAVIGLH------ADDILTVHVGP-VTHRFVKKTVRESIL
GAMMA			
EBV	NP_039908	604	ITPGEEHRLA---GLRPGEDYESFRLTGGV-YHFVKKHVHESFL
CalliHV3	AAK38212	601	VTPGEEGKLR---DLRPGEDYESFSLSGGT-FHFVKKHIHKSFL
BHV-4	AAK07928	600	IQDQNLHLH----HLKPD-DYETFHLSTGP-IHFVKQHKTKSLL
AlHV-1	AAC58060	622	IKQQDLPKFT---NLTAN-DYETFMISGGP-VHFVKKHKTESLL
MHV-68	AAF19277	601	IPDNKLQMFP---NLTPA-DYETFTLPSGT-VHFVKKHKKCSLL
HVS	DJBEM2	594	IPHHALHNYP---HLKSS-DYETFMLSSGP-IHFVKKHIQASLL
AtelHV3	AAC95533	594	IPHNSLHNYP---YLKSS-DYETFMLSSGP-IHFVKKHIQTSLL
HHV-8	AAB62593	605	IPGDSLHLHP---HLSPD-DYETFVLSGGP-VHFVKKHKRESLL
PorcLTHV-1	AAF16520	592	IHHEDLHKYP---QLKEE-DYETFLISSGP-VHFVKKHISESLL
EHV-2	NP_042605	602	IPGDRLCLHP---HLGPG-DYETFELASGP-VHFVKKHKAVSLL
UNCLASSIFIED			

GTHV	AAC26681	14	TRRAETLK-----ELKAGE**D**YEEFKVQGMS-LFYVKPHVRRSLL
TortHV	BAB40430	14	TRNPESLK-----DLKAGK**D**YVSFNVQGHT-LYYVLNHVKQSLL
CCV	NP_041148	664	DSDKTNRV-----GDYMGY**D**WSKIDQGFEK-FTLVLRVDRTDPE
RanHV-1	AAD12269	690	DVRRVAQF-----RGWIVF**D**WRQIEEGFGL-ASLMYTPSKRRFL

Replace the entirety of Table 5 on pages 49-54 with the following new Table 5:

Table 5 - Variable Sequence Marker Codes

ORF 8

CODE **331**

1 **CGTCTCTCGG** (SEQ ID NO:198)

2 **.........A** (SEQ ID NO:199)

ORF 11

CODE **560**

1 **AGAGTCAGTG** (SEQ ID NO:200)

2 **.....A....** (SEQ ID NO:201)

ORF14

CODE	1841	1851	1861	1871	1881	1891	1901	
1	TGCGCCCCAG	C---------CGTGCCGGG	CGTTCCCGCG	TGAGAGTGGA	AGACCAAACT	CTGGAACCAT	CGTCCCCCGC	(SEQ ID NO:202)
1A	....	.---------..........	....	...A......	....	....	....	(SEQ ID NO:203)
1B	....	.---------..........	....	...C......	....	....	....	(SEQ ID NO:204)
2	....	.CGCCCCAGC.........	....	....	....	....	....	(SEQ ID NO:205)
2A	....	.CGCCCCAGC.........	....	...A......	....	....	....	(SEQ ID NO:206)
2B	....	.CGCCCCAGC.........	....	....	....	....	........A.	(SEQ ID NO:207)
3	.......-..	.CGCCCCAGC.........	....	....	....	....	....	(SEQ ID NO:208)

ORF15 **490**

1 **AACCTCGATG** (SEQ ID NO:209)

2 **.....A...** (SEQ ID NO:210)

ORF30-m1

CODE	2251	2261	2271	2281	2291	2301	
1	GTCGACTACT	CGACGTTCGA	GGTGGGTGAC	CAAAAGTTAT	TTTTTGTCCA	CGCCCATATT	(SEQ ID NO:211)
1A	.......C..	....	....	....	....	....	(SEQ ID NO:212)
2	...A......	....	....	....	....	....	(SEQ ID NO:213)
2A	...A......	....	....	....	....	....A.....	(SEQ ID NO:214)
2B	...A......	....	........G.	....	....	....	(SEQ ID NO:215)

ORF30-m2

CODE **2961**

1 **GGCAGCAGAG** (SEQ ID NO:216)

2 **.......A..** (SEQ ID NO:217)

ORF33-m1

CODE **41**

1 **GCAATTGGCG** (SEQ ID NO:218)

2 **..C.....** (SEQ ID NO:219)

ORF33-m2

CODE **2921**

1 **TGGAAAATGA** (SEQ ID NO:220)

2 **.....G....** (SEQ ID NO:221)

ORF34

CODE **151** ^ **191** ^ **301**

1 **CAACAGACAA ^ CGGACGATCT ^ GCCTGCCGGG** (SEQ ID NOs:222, 224 and 226, respectively)

2 **.....T.... ^ .... ^ ....** (SEQ ID NOs:223, 224 and 226, respectively)

2A **.....T.... ^ .... ^ ..A.....** (SEQ ID NOs:223, 224 and 227, respectively)

2B **.....T.... ^ .... ^ ......T...** (SEQ ID NOs:223, 224 and 228, respectively)

3 **.......... ^ ......G... ^ ....** (SEQ ID NOs:222, 225 and 226, respectively)

ORF37

CODE **791** **801** **811** ***821*** ***831*** ***841*** ***851***

1 **GGGCGGCGTC CCTTTTTTCC CCAAAATAAa agccggtgca attaaagacg agtgcccctt tttt-gtcggc** (SEQ ID NO:229)

1A ....t..... (SEQ ID NO:230)
2 ...T..... ....-..... (SEQ ID NO:231)

ORF39

CODE 1311 ^ 1561
1 AATAGTGTCA ^ CCCGAGCCAG (SEQ ID NOs:232 and 234, respectively)
2 ..... ^ .....C. (SEQ ID NOs:232 and 235, respectively)
3 .....T. ^ .....C. (SEQ ID NOs:233 and 235, respectively)

ORF40

CODE 491 ^ 581
1 TCTACACCCC ^ TTGATCGTAT (SEQ ID NOs:236 and 238, respectively)
2 .....T.. ^ .....A... (SEQ ID NOs:237 and 239, respectively)

ORF52

CODE **1151**
1 **GATACGCCAA** (SEQ ID NO:240)
2 **......T...** (SEQ ID NOP:241)

ORF67

CODE **751** **781**
1 **GCCAGGCAGC ^ TCTGCAGAAA** (SEQ ID NOs:242 and 244, respectively)
1A **........A. ^** ..... (SEQ ID NOs:243 and 244, respectively)
2 ..... **^ .T.....** (SEQ ID NOs:242 and 245, respectively)

ORF68

CODE **331** **341** **^ 621** **^ 701** **711** **721** **731** **741** **751**
1 **CATCTCAACT CCAGCCTTAT ^ ATTAGTTCGT ^ GGCGGCCGCT GCCGCGGCGG CGGCCGTCGG AGGGGGGGG-A TGCGCGCCCC**
GAGGCGGCGC (SEQ ID NOs:246, 249 and 251, respectively)
1A .... **^** ..... **^** .... **.....G.** .....
..... (SEQ ID NOs:246, 249 and 252, respectively)
2 .... **^** ..... **^** .... **.....-..** .....
..... (SEQ ID NOs:246, 249 and 251, respectively)
2A .... **^** ..... **^ .....C** .... **.....-..** .....
..... (SEQ ID NOs:246, 249 and 253, respectively)

3 .... ^ .....A. ^ ....T. ....-.. .....
..... (SEQ ID NOs:246, 250 and 254, respectively)
3A .... ^ .....A. ^ .....A .....T. ....-.. .....
..... (SEQ ID NOs:246, 250 and 255, respectively)
4 .... ^ .....A. ^ ....-.. .....
..... (SEQ ID NOs:246, 250 and 251, respectively)
4A ....A..... ^ .....A. ^ ....-.. .....
..... (SEQ ID NOs:247, 250 and 251, respectively)
4B .... ^ .....A. ^ ....-.. .....
....T..... (SEQ ID NOs:246, 250 and 256, respectively)
5 .... ^ .....A. ^ .....G ..A..... ....-.. .....
..... (SEQ ID NOs:246, 250 and 257, respectively)
6 .....T.... ..... ^ .....A. ^ ....-.. .....
....T..... (SEQ ID NOs:248, 250 and 256, respectively)

ORF73

CODE **360**
1 **CAATGCCTCT** (SEQ ID NO:258)
2 .....T.... (SEQ ID NO:259)